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Research

Manual lymph drainage may not have a preventive effect on the development of breast cancer-related lymphoedema in the long term: a randomised trial

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KEY WORDS

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ABSTRACT

Question: What are the short-term and long-term preventive effects of manual lymph drainage (MLD), when used in addition to information and exercise therapy, on the development of lymphoedema after axillary dissection for breast cancer? **Design**: Randomised controlled trial with concealed allocation, blinded assessors and intention-to-treat analysis. **Participants**: Adults undergoing unilateral dissection for breast cancer were recruited, with 79 allocated to the experimental group and 81 to the control group. **Intervention**: The experimental group received guidelines about prevention of lymphoedema, exercise therapy and MLD. The control group received the same guidelines and exercise therapy, but no MLD. The interventions in both groups were delivered for 6 months. **Outcome measures**: The primary outcome was cumulative incidence of arm lymphoedema defined in four ways ($\geq$ 200 ml, $\geq$ 2 cm, $\geq$ 5%, and $\geq$ 10% increase), which represent the difference in arm volume or circumference between the affected and healthy sides compared with the difference before surgery. Secondary outcomes included point prevalence of lymphoedema, change in arm volume difference, shoulder range of movement, quality of life and function. **Results**: Incidence rates were comparable between experimental and control groups at all follow-up measurements. Sixty months after surgery, the cumulative incidence rate for the $\geq$ 200 ml definition was 35% for the experimental group versus 29% for the control group (RR 0.89, 95% CI 0.51 to 1.54, $p = 0.45$); for the $\geq$ 2 cm definition 35% versus 38% (RR 0.93, 95% CI 0.59 to 1.45, $p = 0.73$); for the $\geq$ 5% definition 68% versus 53% (RR 1.28, 95% CI 0.97 to 1.69, $p = 0.08$) and for the $\geq$ 10% definition 28% versus 24% (RR 1.18, 95% CI 0.66 to 2.10, $p = 0.57$). The secondary outcomes were comparable between the groups at most assessment points. **Conclusion**: Manual lymph drainage may not have a preventive effect on the development of breast cancer-related lymphoedema in the short and long term. **Trial registration**: Netherlands Trial Register NTR 1055. **[Devoogdt N, Geraerts I, Van Kampen M, De Vrieze T, Vos L, Neven P, Vergote I, Christiaens M-R, Thomis S, De Groef A (2018) Manual lymph drainage may not have a preventive effect on the development of breast cancer-related lymphoedema in the long term: a randomised trial. *Journal of Physiotherapy* 64: 245–254]**

Introduction

Among all cancers, breast cancer is the most frequent type in females. In 2012, 1.7 million women were diagnosed with breast cancer worldwide. Due to the evolution in diagnostic and treatment techniques, the survival rate is increasing.[1] Consequently, complications related to the treatment of breast cancer have gained importance. Lymphoedema is one of the most feared complications. Lymphoedema is caused by a reduced transport capacity of the lymph system (related to the surgery, radiotherapy, or both), sometimes combined with an increase in lymph load (eg, related to infection).[2,3] Lymphoedema can cause functional impairments[4] and psychosocial morbidities,[5] and may lead to diminished health-related quality of life.[6,7]

Although the majority of patients seem to develop breast cancer-related lymphoedema before 12 to 24 months postoperatively,[8,9] breast cancer survivors have a lifelong risk of developing lymphoedema.[10] Incidence rates of lymphoedema vary among studies, with an overall incidence of 21%.[11] Prospective studies have described a cumulative incidence of 10% at 2 years,[12] between 21 and 54% at 3 years,[7] and between 16 and 94% at 5 years post-surgery.[8,12,13]

Lymphoedema can be diagnosed using a wide spectrum of subjective and objective measurement methods. Subjective

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findings include self-report of symptoms of heaviness, pain and swelling, which are moderately reliable.[14,15] The most commonly used measurements of limb volume are the circumference measurement and the water displacement method.[16] The perimeter and volumeter are reliable measurement devices to assess arm circumferences and volumes, respectively.[17,18] A difference of $\geq$ 200 ml or $\geq$ 2 cm compared to the pre-surgical value are frequently reported as lymphoedema.[14,19] However, a study demonstrated the superiority of relative arm size changes (5% and 10%), since they take into account the arm volume of the patient at baseline.[20] The same absolute change of arm volume difference has a greater impact in a patient with low body weight (and a small arm volume) than a patient with high body weight (and a larger arm volume). A frequently occurring complication after lymph node dissection for breast cancer is decreased shoulder range of motion.[21] For people with breast cancer-related lymphoedema, the SF-36 and Lymph-ICF questionnaires are reliable and valid questionnaires for assessing health-related quality of life on the one hand and associated problems in functioning on the other hand.[22,23]

Prevention of lymphoedema is an important issue. By application of manual lymph drainage (MLD) immediately after axillary dissection, development of lymphoedema may be prevented. The aim of this 'preventive MLD' is to stimulate rerouting of the lymphatic system after lymph node dissection and to eliminate accumulated water and proteins out of the interstitial tissue. The randomised controlled trial by Lacomba et al (n = 120) showed that the combination of MLD, exercise therapy and information resulted in a lower incidence of arm lymphoedema than information alone.[24] Yet, the contribution of MLD on the prevention of arm lymphoedema cannot be derived from this study. So far, two randomised controlled trials have investigated the preventive effect of MLD, as a unique treatment modality, additional to another physical treatment.[25] The study by Devoogdt et al (n = 160) found that when MLD was added to exercise therapy and information, it was unlikely to be effective for the prevention of lymphoedema.[26] In contrast, the randomised controlled trial by Zimmermann et al (n = 67) reported that the addition of MLD to information and exercises was effective.[27] The Cochrane systematic review by Stuiver et al investigated 10 aspects of risk of bias in both studies. They concluded that the risk of bias in the trial by Zimmermann was high, whereas the risk of bias in the trial by Devoogdt was moderate.[25] Follow-up was short to moderate and ranged from 6 to 12 months in these studies.[25–27]

The preventive effect of MLD on the development of breast cancer-related lymphoedema in the long term has never been examined. It is important to investigate whether there is a long-term preventive effect because a treatment immediate post-surgery may result in prevention of lymphoedema later on during the postoperative period. This has been shown in the study by Lacomba.[24] Immediately after surgery, participants received nine sessions over 3 weeks of information (control group) or information, exercises and MLD (experimental group). The first participant in that study developed lymphoedema 7 months after surgery and most who developed it did so between 10 and 12 months after surgery. The participants were not followed beyond 12 months. It is important to continue the follow-up beyond 12 months because 20 to 33% of patients with breast cancer who develop arm lymphoedema will do so more than 12 months after surgery.

The above-mentioned study by Devoogdt et al[26] followed participants beyond 12 months after their surgery. The previous publication presented the short-term (up to 1 year) effects of MLD.[26] The aim of the present report is to examine the long-term, preventive effects (up to 5 years after surgery) of MLD.

Therefore, the research question for this trial was:

> What are the short-term and long-term preventive effects of manual lymph drainage when used in addition to information and exercise therapy on the development of lymphoedema after axillary dissection for breast cancer?

Method

Design

A randomised controlled trial was performed with concealed allocation, blinded outcome assessment, and intention-to-treat analysis. Participants were enrolled at the time of axillary dissection for breast cancer. After baseline assessment, participants were individually randomised into either an experimental group or a control group. Concealed allocation was achieved by having randomisation performed by a researcher who was not involved in the recruitment and treatments of participants. Four permuted blocks were used to stratify randomisation by body mass index ($\leq$ 25 versus $>$ 25 kg/m^2) and by axillary irradiation (yes/no) because these are the most important risk factors for the development of breast cancer-related lymphoedema.[7,14,28] Postoperatively, participants in both groups were prescribed exercise therapy and provided with information about prevention of lymphoedema. In addition, participants randomised to the experimental group received manual lymph drainage. Participants in both groups were assessed, by a researcher who was unaware of the randomised group allocations, for the development of lymphoedema at 6, 12, 24 and 60 months after their surgery.

Participants, therapists, centre

All patients with operable breast cancer and scheduled for unilateral surgery at the Multidisciplinary Breast Centre of the University Hospitals Leuven between October 2007 and February 2009 were assessed for study eligibility prior to surgery. Only patients with a unilateral axillary dissection levels I, I–II or I–III were included in the study. Patients were excluded if they: had a sentinel procedure on the contralateral side; were physically or mentally unable to participate; were not interested; or had breast cancer metastasis at first diagnosis.

All treatments (information, exercise therapy and MLD) were performed by four therapists. Two of the therapists had undergone MLD training with the Leduc method, and the two other therapists had undergone MLD training with the Vodder method.

Intervention

Both groups

During hospitalisation, participants received the following information about the prevention of lymphoedema: elevate the arm in case of heaviness, avoid lifting heavy objects, use the arm in daily life as normally as possible, avoid limb constriction, avoid extremes of temperature, apply skin care, and avoid an increase in body weight.[29] These guidelines were outlined in a brochure and, when requested, patients could obtain more information during the exercise therapy sessions.

Participants were also prescribed exercise therapy, which was started during hospitalisation with low level mobilising exercises for the hand, elbow and shoulder. After hospitalisation, 30-minute individual exercise sessions were provided at the Department of Physical Medicine and Rehabilitation of the University Hospitals Leuven. These sessions consisted of: passive mobilisation of the shoulder; stretching and transverse strain of the breast muscles; scar tissue massage; and active mobilising and stabilising exercises.[26] In the beginning, participants were seen twice a week and frequency was gradually diminished to once every 2 weeks, over a total treatment period of 6 months.

A participant who developed lymphoedema (defined as an increase of 200 ml or more in arm volume compared with baseline) in either group had to wear an inelastic bandage. When the

lymphoedema was maximally diminished, this bandage was replaced by a custom-made sleeve.

Experimental group only

Only the participants in the experimental group received standardised MLD. One week after the removal of axillary drains, MLD was started for a period of 20 weeks. During this period, 40 30-minute sessions were scheduled. Frequency was increased from one to three times a week, and then decreased to once a week. During MLD, neck and axillary lymph nodes were emptied, axilloaxillary anastomoses at the breast and back and lymphatics at the lateral side of the shoulder (Mascagni pathway) were stimulated, and the arm and hand were drained from proximal to distal.

Outcome measures

The primary and secondary outcome measures, their definitions, and their methods of measurement are presented in Tables 1 and 2.

Data analysis

It was estimated that 30% of the control group would developed arm lymphoedema in the first year.[8,30] It was hypothesised that a 20% reduction in the incidence rate of lymphoedema (resulting in an incidence rate of 10% in experimental group) would be clinically important. Assuming a two-sided α of 0.05, power of 80%, and a 5% drop-out rate, a sample size of 160 patients was required to detect this clinically important difference based on a comparison of two proportions.

The baseline characteristics of the participants were summarised using descriptive statistics and tabulated for comparison between groups. To analyse whether the study participants were representative of the population from which they were recruited, baseline patient characteristics were compared between included and excluded patients. Independent *t*-test and Mann-Whitney U test were used to compare continuous variables and the Chi-squared test to compare nominal variables.

The primary intention-to-treat analyses compared the groups regarding cumulative incidence of lymphoedema for the four definitions of arm lymphoedema from baseline up to 60 months post-surgery using a Chi-squared test. A similar approach was used for point prevalence of objective and subjective lymphoedema, which were secondary outcomes. Mann-Whitney U test was used to compare absolute and relative changes in arm volume, health-related quality of life and problems in functioning associated with the development of arm lymphoedema. All analyses were conducted using commercial statistical software.[a]

Results

Flow of participants through the study

Of the 337 patients who were screened, 160 were included in the present study. Among these, 79 participants were randomised to the experimental group and 81 to the control group. The flow of participants through the study is presented in Figure 1. Summary data are presented in Tables 2 to 8, with de-identified individual participant data available in Table 9 on the eAddenda.

Characteristics of the participants

Compared with non-participating (excluded) patients, the study participants were 2.8 years younger ($p = 0.04$), had 1.3 higher body mass index ($p = 0.02$), less often received axillary irradiation (8% versus 16%, $p = 0.03$), and more often received chemotherapy (68% versus 58%, $p = 0.06$). All other characteristics related to disease and treatment, such as number and levels of lymph nodes dissected, type of breast surgery, surgery at the dominant side, tumour size, lymph node stage, radiotherapy of the internal mammary chain and medial supraclavicular region, target therapy and endocrine treatment, were comparable between groups (data not shown).

Baseline characteristics of the participants and their surgery are presented in Table 3. These data show that the randomised groups were comparable at baseline. Four patients in the experimental group and two in the control group had developed arm lymphoedema (increase of ≥ 200 ml) before the start of the treatment period. Two patients in the experimental group and three in the control group developed deep venous thrombosis in the healthy arm.

Table 1
Primary outcomes of the study, including definitions, measurement times, measurement methods and calculations.

Definition	Time relative to surgery *(months)*	Material	Method	Calculation
Cumulative incidence of arm lymphoedema defined as ≥ 200 ml increase of absolute arm volume difference compared to pre-surgical value	Pre, 6, 12, 24, 60	Volumeter, weighing balance and receptacle	Water displacement method up to 16 cm above olecranon of arm at affected and healthy side[18]	Absolute arm volume difference = arm volume affected side – arm volume healthy side Absolute change of arm volume difference = absolute volume difference at assessment – absolute volume difference at baseline
Cumulative incidence of arm lymphoedema defined as ≥ 2 cm increase of arm circumference difference at two adjacent measurement points compared to pre-surgical value	Pre, 6, 12, 24, 60	Perimeter	Circumferences at olecranon and 4, 8, 12, 16 and 20 cm above and under olecranon of arm on the affected and healthy side[17]	Arm circumference difference = circumference affected side – circumference healthy side Change of arm circumference difference = arm circumference difference at assessment – circumference difference at baseline
Cumulative incidence of arm lymphoedema defined as $\geq 5\%$ or $\geq 10\%$ increase of relative arm volume difference compared to pre-surgical value	Pre, 6, 12, 24, 60	Volumeter, weighing balance and receptacle	Water displacement method up to 16 cm above olecranon of affected and healthy arm[18]	Relative arm volume difference = (absolute volume difference/arm volume healthy side) $\times$ 100 Relative change of arm volume difference = relative volume difference at assessment – relative volume difference at baseline

Table 2
Secondary outcomes of the study, including definitions, measurement times, measurement methods and calculations.

Definition	Time relative to surgery *(months)*	Material	Method	Calculation
Point prevalence of arm lymphoedema, defined using each method presented in Table 1	Pre, 6, 12, 24, 60	See Table 1	See Table 1	See Table 1
Point prevalence of subjective arm and trunk lymphoedema	6, 12, 24, 60	Questioned at interview	Arm: Oedema at hand or arm? Trunk: Oedema at scapular region, side of trunk or breast region?	N/A
Absolute and relative change of arm volume difference	Pre, 6, 12, 24, 60	Volumeter, weighing balance and receptacle	Water displacement method up to 16 cm above olecranon of affected and healthy arm	Absolute change of arm volume difference = absolute volume difference at assessment – absolute volume difference at baseline Relative change of arm volume difference = relative volume difference at assessment – relative volume difference at baseline
Change of shoulder range of flexion and abduction	Pre, 6, 12, 24, 60	Goniometer	Goniometry with participant sitting erect	Change of range of movement = range of affected side at assessment – range of affected side at baseline
Change of shoulder range of external and internal rotation	Pre, 6, 12, 24, 60	Tape measure	Distance between finger and C7[41]	Change of range of movement = range of affected side at assessment – range of affected side at baseline
Health-related quality of life	6, 12, 24, 60	SF-36 on paper[23]	Completion by participant	Mental health score, physical health score
Problems in functioning	12, 24, 60	Lymph-ICF on paper[22]	Completion by participant	Total score, physical function score, mental function score, household activities score, mobility activities score, and life and social activities score

Compliance with the study protocol

As discussed above, MLD was due to start 1 week after removal of the axillary drains. Axillary drains took approximately 4 weeks (SD 1.5) to be removed, so MLD started in the experimental group after approximately 5 weeks (SD 1.5).

Participants had reasonable compliance with their allocated interventions, as shown in Table 4. In the experimental group, 11 participants (15%) received 23 to 29 manual lymph drainage sessions, 26 participants (36%) received 30 to 35 sessions, and 36 participants (49%) received more than 35 sessions. The main reason for absence during the therapy sessions was illness related to chemotherapy and/or radiotherapy. Other reasons were problems with transport, holiday, and illness from other causes.

After the 6 months of standardised treatment at the study site, 57 participants continued physiotherapy treatment outside the hospital. Of them, 44 had developed lymphoedema: 39 received MLD for treatment of lymphoedema (26 in the experimental group and 13 in the control group; median number of sessions: 53), 14 continued exercise therapy (median number of sessions: 43), and 30 wore a compression garment. The other 13 participants, without diagnosis of lymphoedema, received MLD for preventive purposes (five in the experimental group and five in the control group; with a median of 43 sessions) and/or continued exercise therapy (eight participants).

Primary outcomes

The cumulative incidence rates of arm lymphoedema at the different time intervals after surgery are compared between the experimental and control groups in Figure 2. No significant differences were found for the different assessment times for cumulative incidence rates of arm lymphoedema using the four definitions of lymphoedema (ie, $\geq$ 200 ml increase, $\geq$ 2 cm increase, $\geq$ 5% increase, $\geq$ 10% increase). When the results were compared between groups using relative risk, the confidence intervals were wide, as shown in Table 5.

The cumulative incidence data generated when lymphoedema was defined as a $\geq$ 5% increase were re-analysed after the exclusion of participants who had only transient lymphoedema. Transient lymphoedema was defined as oedema that was present at 1, 3 or 6 months after surgery and not present at 12, 24 and 60 months after surgery. Therefore, only the results for 12, 24 and 60 months after surgery were relevant. After the exclusion of participants with transient lymphoedema, the results were similar, as shown in Figure 3. The relative risk (95% CI) between groups was 1.11 (0.64 to 1.91) at 12 months, 0.85 (0.56 to 0.44) at 24 months, and 1.08 (0.74 to 1.58) at 60 months.

Secondary outcomes

The point prevalence of arm lymphoedema at the different time intervals after surgery are compared between the experimental and control groups in Figure 4. No significant differences were found for the different assessment times for cumulative incidence rates of arm lymphoedema using the four objective definitions of lymphoedema (ie, $\geq$ 200 ml increase, $\geq$ 2 cm increase, $\geq$ 5% increase, $\geq$ 10% increase) or the two subjective definitions (arm oedema and trunk oedema). When the results were compared between groups using relative risk, the confidence intervals were wide, as shown in Table 6.

Absolute and relative changes in arm volume and change of shoulder range of movement were comparable between the experimental and control groups for each follow-up measurement. These results are presented in Table 7.

Data from the quality of life tools are presented in Table 8. On the mental and physical health domains of the SF-36, the experimental and control groups had comparable results at all follow-up measurement points. Similarly, the physical and mental function domains of the Lymph-ICF also did not differ significantly between the experimental and control groups. In contrast, the household, mobility and life/social activity domains did show a statistically significant difference at 60 months only. The experimental group had higher household, mobility and life/social activities scores (indicating more problems in functioning) than

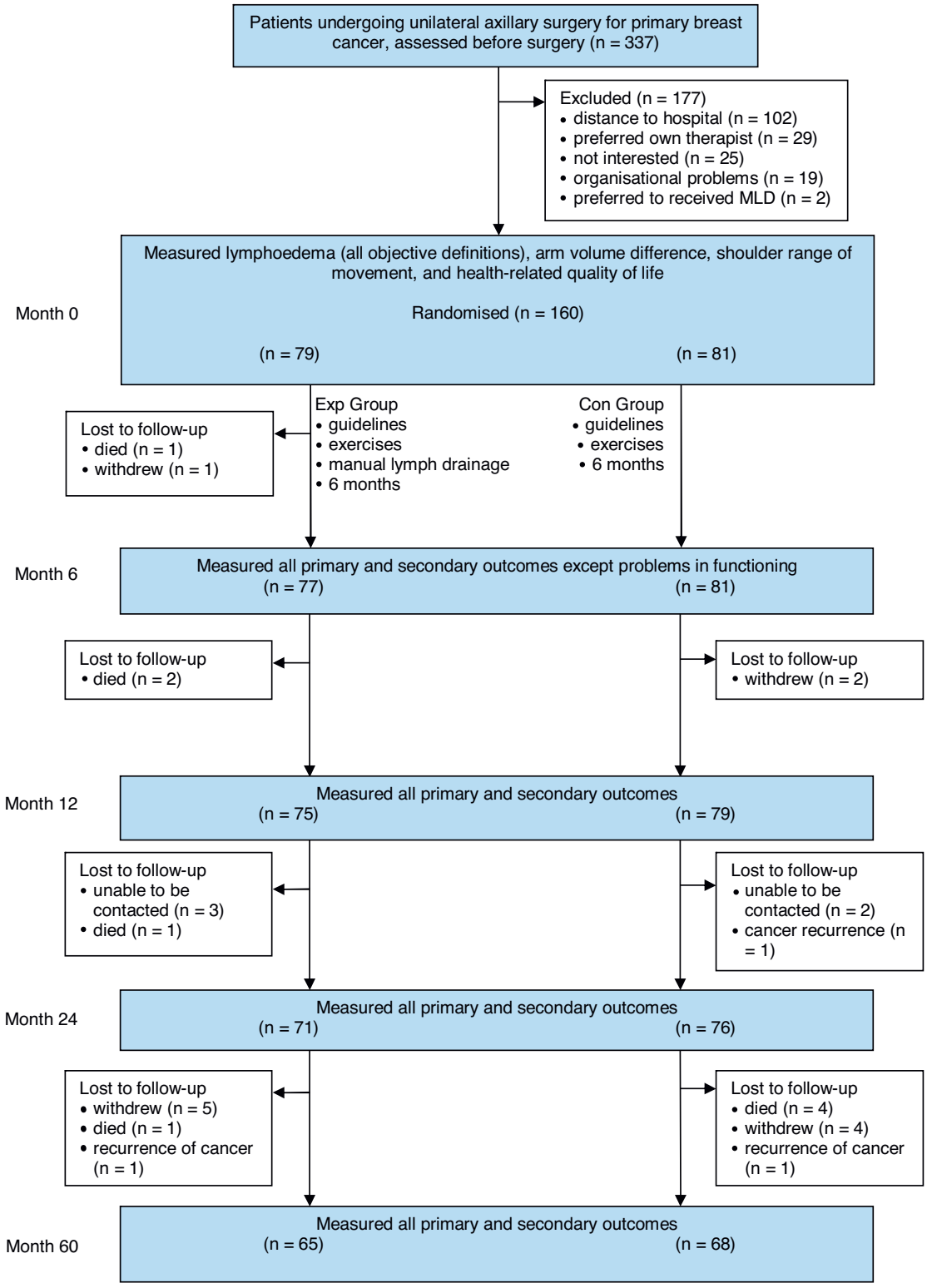

Figure 1. Design and flow of participants through the trial.
Con = control group, Exp = experimental group, MLD = manual lymph drainage.

the control group. The median differences on these domains were 10, 10 and 3 points, respectively. No significant difference was present at 12 or 24 months after surgery.

After the 6 months of physical treatment in the study, 43% of the participants consulted a physiotherapist to continue the sessions. Those with objective lymphoedema were advised to follow decongestive lymphatic therapy, as recommended by the International Society of Lymphology.[31] Forty-four (of 78) participants with lymphoedema followed this advice. In the group without lymphoedema, five participants who received MLD during the study period (experimental group) continued MLD and five in the control group started MLD.

Discussion

This is the first study to examine the short-term and long-term preventive effects of MLD on the development of breast cancer-related lymphoedema. When added to information and exercise

Table 3
Baseline characteristics of participants, therapists and centres.

Characteristic	Exp (n = 79)	Con (n = 81)
Age *(yr)*, mean (SD)	56 (13)	55 (11)
Gender, n female (%)	78 (99)	80 (99)
Body mass index, mean (SD)	26.6 (5.4)	26.2 (5.4)
Increase in arm volume before starting allocated treatment *(%)*, median (IQR)	8 (−34 to 56)	8 (−16 to 64)
Time between surgery and starting allocated treatment *(days)*, mean (SD)	40 (8)	34 (12)
Lymph nodes removed *(n)*, mean (SD)	19 (6)	18 (6)
Type of breast surgery, n (%)		
mastectomy	52 (66)	56 (69)
breast conserving	27 (34)	25 (31)
Surgery on dominant side, n (%)	47 (60)	44 (54)
Level of axillary surgery, n (%)		
I	2 (3)	0 (0)
I–II	43 (54)	54 (67)
I–III	34 (43)	27 (33)
Tumour size, n (%)		
pT0	1 (1)	0 (0)
pT1	21 (27)	26 (32)
pT2	38 (48)	39 (48)
pT3	13 (17)	12 (15)
pT4	6 (8)	4 (5)
Lymph node stage, n (%)		
pN0	23 (29)	25 (31)
pN1	36 (46)	39 (48)
pN2	11 (14)	9 (11)
pN3	9 (11)	8 (10)
Radiotherapy		
intramammary chain, medial supraclavicular	69 (87)	67 (83)
axilla	8 (10)	5 (6)
Chemotherapy		
all	50 (63)	58 (72)
neo-adjuvant	14 (18)	14 (17)
taxane-based	45 (57)	46 (57)
Target therapy	14 (18)	7 (9)
Endocrine treatment	55 (70)	66 (82)

Exp = experimental group, Con = control group.

Table 4
Adherence of participants to their allocated interventions.

Adherence *(sessions)*, mean (SD)	Exp (n = 79)	Con (n = 81)
Exercise	28 (6)	28 (8)
Manual lymph drainage	34 (7)	0 (0)

Exp = experimental group, Con = control group.

therapy, MLD may not have a preventive effect in the short term nor in the long term. After 6 months of treatment and at the different follow-up assessments up to 60 months after axillary dissection, cumulative incidence rates for the different definitions of lymphoedema (ie, the primary outcomes) were comparable between the experimental group (receiving guidelines, exercise therapy and MLD) and the control group (receiving guidelines and exercise therapy). Cumulative incidence reflected the total number of participants who developed arm lymphoedema during the time interval and consequently was the best parameter to investigate prevention of lymphoedema.[32]

Only one other study, by Zimmermann et al,[27] has examined the preventive effect of MLD and followed participants during the treatment period of 6 months. In contrast to the current study, Zimmermann et al concluded that the addition of MLD to exercises is effective to prevent arm lymphoedema. In their study, none of the participants in the group with preventive MLD (0%) had developed lymphoedema 6 months after surgery (defined as a $\geq$ 5% increase), while 70% developed lymphoedema in the group with self-MLD. It is surprising that 6 months after surgery many more participants in their control group had developed arm lymphoedema compared to the current control group (33% with $\geq$ 5% increase). This is especially so because half of their participants did not undergo axillary lymph node dissection, but instead had a sentinel node procedure; in contrast, all of the current participants received axillary lymph node dissection. Many studies have already proven that patients receiving an axillary lymph node dissection are at higher risk of developing arm lymphoedema compared to those receiving a sentinel procedure.[33] Two differences in the methodology between the study by Zimmerman et al and the present study might explain the discrepancy in effectiveness of MLD. Firstly, Zimmermann et al started MLD from the second day after surgery with a frequency of five times a week. In the present study, MLD was applied from approximately 5 weeks after surgery with a gradual increase in the frequency from one to three times a week. Secondly, the method of MLD differed. Zimmermann et al applied a modification of the Földi method, whereas in the present study the Leduc or Vodder methods were applied. The influence of these two items has to be further examined.

Studies have shown that some people who have had breast cancer develop, during the postoperative period, transient arm lymphoedema associated with taxane-based chemotherapy.[34–36] When applied to prevent development of arm lymphoedema, MLD probably has no impact on this lymphoedema evoked by the application of taxanes. However, in the present study, when only the participants with persistent objective arm lymphoedema were analysed at 12, 24 and 60 months after surgery, comparable incidence rates in the experimental and control groups were still observed.

In addition, in the present study, secondary outcome parameters, including shoulder range of movement and health-related quality of life, did not show any benefit from the experimental intervention. Indeed, participants in the experimental group had significantly higher problems in functioning related to development of lymphoedema (for household, mobility and life and social activities). However, the difference between groups was not

Table 5
Cumulative number of participants (%) in each group with lymphoedema defined according to each the study's four objective definitions, and relative risk (95% CI) between groups.

Cumulative incidence of lymphoedema	Groups								Relative risk (95% CI)			
	Month 6		Month 12		Month 24		Month 60		Exp relative to Con			
	Exp (n = 77)	Con (n = 81)	Exp (n = 75)	Con (n = 79)	Exp (n = 71)	Con (n = 76)	Exp (n = 65)	Con (n = 68)	Month 6	Month 12	Month 24	Month 60
$\geq$ 200 ml increase	11 (14)	12 (15)	18 (24)	15 (19)	19 (27)	18 (24)	23 (35)	20 (29)	0.96 (0.45 to 2.05)	1.26 (0.69 to 2.32)	1.13 (0.65 to 1.97)	0.89 (0.51 to 1.54)
$\geq$ 2 cm increase	12 (16)	11 (14)	20 (27)	17 (21)	22 (31)	27 (36)	23 (35)	26 (38)	1.15 (0.54 to 2.44)	1.23 (0.70 to 2.18)	0.87 (0.55 to 1.38)	0.93 (0.59 to 1.45)
$\geq$ 5% increase	30 (39)	27 (33)	38 (51)	31 (39)	38 (53)	37 (49)	44 (68)	36 (53)	1.17 (0.77 to 1.77)	1.29 (0.91 to 1.84)	1.10 (0.80 to 1.51)	1.28 (0.97 to 1.69)
$\geq$ 10% increase	9 (12)	11 (14)	16 (21)	14 (18)	17 (24)	16 (21)	18 (28)	16 (24)	0.86 (0.38 to 1.96)	1.20 (0.63 to 2.29)	1.14 (0.62 to 2.07)	1.18 (0.66 to 2.10)

Exp = experimental group, Con = control group.

Table 6
Point prevalence presented as number (%) of participants in each group for lymphoedema defined according to each the study's four objective and two subjective definitions, and relative risk (95% CI) between groups.

Point prevalence of lymphoedema	Groups								Relative risk (95% CI)			
	Month 6		Month 12		Month 24		Month 60		Exp relative to Con			
	Exp (n = 77)	Con (n = 81)	Exp (n = 75)	Con (n = 79)	Exp (n = 71)	Con (n = 76)	Exp (n = 65)	Con (n = 68)	Month 6	Month 12	Month 24	Month 60
≥ 200 ml increase	4 (5)	8 (10)	9 (12)	8 (10)	11 (15)	11 (14)	16 (24)	12 (17)	0.53 (0.17 to 1.68)	1.19 (0.48 to 2.91)	1.07 (0.50 to 2.31)	1.39 (0.72 to 2.72)
≥ 2 cm increase	6 (8)	8 (10)	11 (15)	8 (10)	14 (20)	10 (13)	14 (22)	14 (21)	0.79 (0.29 to 2.17)	1.44 (0.62 to 3.40)	1.50 (0.71 to 3.15)	1.05 (0.54 to 2.02)
≥ 5% increase	17 (22)	17 (21)	20 (27)	18 (23)	16 (23)	27 (36)	21 (33)	20 (30)	1.05 (0.58 to 1.91)	1.17 (0.67 to 2.03)	0.63 (0.37 to 1.07)	1.10 (0.66 to 1.82)
≥ 10% increase	5 (6)	5 (6)	9 (12)	6 (8)	11 (15)	9 (12)	12 (19)	8 (12)	1.05 (0.32 to 3.49)	1.58 (0.59 to 4.22)	1.03 (0.58 to 2.97)	1.56 (0.69 to 3.59)
Subjective arm oedema	13 (17)	8 (10)	18 (24)	14 (18)	23 (32)	21 (28)	28 (43)	24 (35)	1.71 (0.75 to 3.90)	1.35 (0.73 to 2.52)	1.17 (0.71 to 1.92)	1.22 (0.80 to 1.87)
Subjective trunk oedema	28 (36)	22 (27)	20 (27)	22 (28)	21 (30)	22 (29)	9 (14)	12 (28)	1.34 (0.84 to 2.13)	0.96 (0.57 to 1.61)	1.02 (0.62 to 1.69)	0.78 (0.35 to 1.74)

Exp = experimental group, Con = control group.

Table 7
Median (IQR) for changes in arm volume and shoulder range of movement in each group and the Mann-Whitney U test result for the between-group comparison.

Outcome	Groups								Mann-Whitney U test			
	Month 6		Month 12		Month 24		Month 60		*p*-value			
	Exp (n = 77)	Con (n = 81)	Exp (n = 75)	Con (n = 79)	Exp (n = 71)	Con (n = 76)	Exp (n = 63)	Con (n = 66)	Month 6	Month 12	Month 24	Month 60
Absolute change in difference in arm volume *(ml)*	58 (7 to 110)	31 (−17 to 98)	34 (−29 to 130)	45 (−21 to 90)	32 (−15 to 113)	66 (12 to 136)	54 (−5 to 147)	44 (−11 to 143)	0.41	0.97	0.13	0.59
Relative change in difference in arm volume *(%)*	2.1 (0.3 to 4.8)	1.5 (−0.8 to 4.5)	1.9 (−1.4 to 5.4)	2.0 (−1.0 to 4.4)	1.7 (−0.5 to 4.8)	3.1 (0.7 to 6.2)	2.9 (−0.1 to 7.5)	2.3 (−0.4 to 6.1)	0.44	0.98	0.12	0.44
Change in shoulder range												
Flexion *(deg)*	1 (−7 to 5)	0 (−9 to 4)	0 (−8 to 6)	0 (−8 to 5)	−5 (−11 to 4)	−2 (−8 to 3)	−5 (−15 to 7)	−7 (−14 to 3)	0.78	0.72	0.27	0.98
Abduction *(deg)*	0 (−4 to 3)	0 (−2 to 2)	0 (−4 to 2)	0 (0 to 5)	0 (−6 to 2)	0 (−4 to 8)	−2 (−9 to 0)	−2 (−12 to 4)	0.87	0.72	0.05	0.91
External rotation *(cm)*	0.3 (−1.5 to 0.5)	−0.4 (−1.5 to 0.4)	−0.2 (−1.9 to 1.1)	−0.4 (−1.2 to 0.8)	−0.8 (−2.0 to 0.6)	−1.6 (−2.5 to 1.3)	−1.2 (−3.6 to 1.2)	−1.8 (−3.0 to 0.5)	0.55	0.86	0.05	0.26
Internal rotation *(cm)*	0.5 (−1.0 to 2.4)	0.6 (−0.5 to 3.5)	1.0 (−1.3 to 3.7)	0.5 (−1.2 to 2.2)	−0.3 (−2.5 to 3.7)	−0.5 (−2.6 to 1.2)	0.1 (−2.1 to 1.7)	0.15 (−2.5 to 2.3)	0.25	0.48	0.45	0.96

Exp = experimental group, Con = control group.

Table 8
Median (IQR) for quality of life domains in each group and the Mann-Whitney U test result for the between-group comparison.

Quality of life domain	Groups								Mann-Whitney U test			
	Month 6		Month 12		Month 24		Month 60		*p*-value			
	Exp (n = 77)	Con (n = 81)	Exp (n = 75)	Con (n = 79)	Exp (n = 70)	Con (n = 76)	Exp (n = 65)	Con (n = 67)	Month 6	Month 12	Month 24	Month 60
SF-36 *(0 to 100)*												
Mental health	74 (47 to 89)	69 (53 to 86)	80 (54 to 90)	82 (59 to 90)	81[a] (68 to 90)	81[b] (67 to 90)	78[a] (56 to 88)	81 (65 to 91)	0.56	0.70	0.95	0.15
Physical health	63 (42 to 82)	58 (46 to 81)	74 (50 to 88)	78 (52 to 88)	75[a] (56 to 89)	80[b] (60 to 90)	78[a] (46 to 87)	77 (61 to 92)	0.78	0.50	0.28	0.09
Lymph-ICF *(0 to 100)*[c]												
Physical function			13 (4 to 24)	14 (7 to 33)	13 (4 to 32)	10 (3 to 24)	16 (4 to 29)	7 (3 to 24)		0.22	0.22	0.12
Mental function			6 (1 to 18)	7 (0 to 27)	5 (0 to 21)	3 (0 to 8)	2 (0 to 14)	2 (0 to 11)		0.47	0.24	0.47
Household activities			11 (0 to 29)	12 (1 to 35)	15 (4 to 38)	9 (2 to 26)	16 (4 to 36)	6 (0 to 21)		0.85	0.10	0.02
Mobility activities			15 (6 to 38)	13 (3 to 39)	16 (5 to 36)	10 (3 to 18)	16 (6 to 36)	6 (0 to 23)		0.68	0.11	0.01
Life/social activities			8 (2 to 25)	10 (1 to 29)	9 (3 to 25)	5 (0 to 21)	6 (2 to 17)	3 (0 to 10)		0.92	0.18	0.03

Exp = experimental group, Con = control group.
[a] One missing.
[b] Two missing.
[c] Lower scores are better.

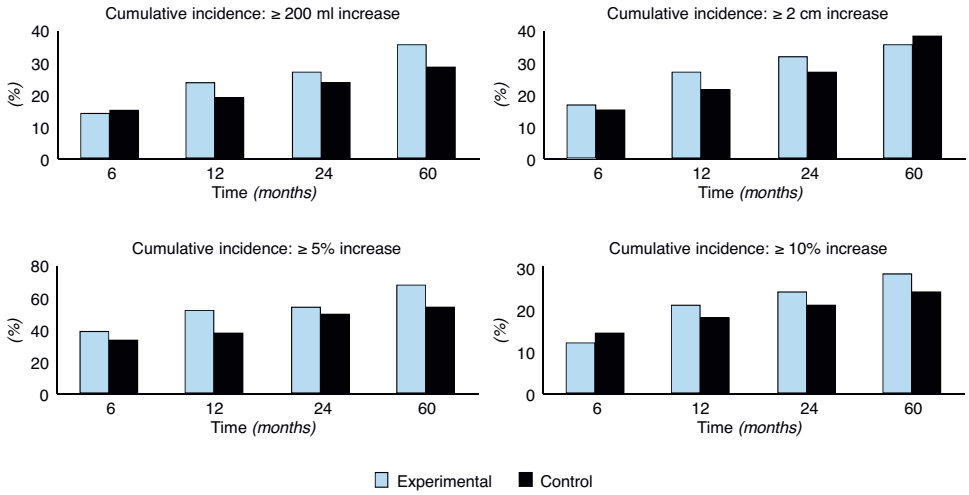

Figure 2. Cumulative incidence rates (%) of objective arm lymphoedema for the four definitions at different time intervals after surgery (months), with comparison between intervention group with manual lymph drainage (blue bar) and control group without manual lymph drainage (black bar).

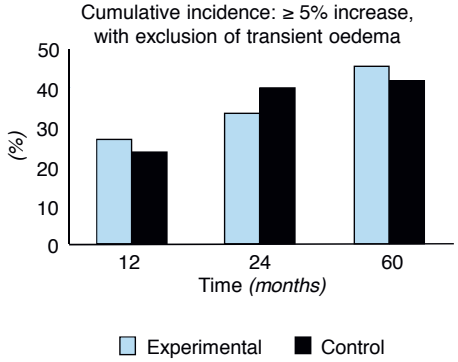

Figure 3. Cumulate incidence rate (%) of objective arm lymphoedema at 12, 24 and 60 months after surgery, with exclusion of transient lymphoedema. Comparison between intervention group with manual lymph drainage (blue bar) and control group without manual lymph drainage (black bar).

clinically relevant. At 60 months after surgery, participants in the experimental group scored 10 points higher (ie, worse) on the household activities and mobility activities domain, and 3 points higher on the life and social activities domain, whereas the clinically important differences for these three domains are 21, 21 and 34, respectively.[22]

The present study had several strengths. Participants were measured before surgery using the water displacement method and circumference measurements. These preoperative measurements allowed natural differences in arm volume to be determined before surgery. At each follow-up measurement, the difference in arm volume between the affected and non-affected arms was compared with the preoperative difference. This was done to control for the patients' change in weight. Four different criteria to define lymphoedema were used: $\geq$ 200 ml increase, $\geq$ 2 cm increase, and $\geq$ 5% and 10% increase. The 5% and 10% criteria were added after the study was registered because a subsequent study highlighted the benefit of relative criteria (ie, they are independent of body size and thus uninfluenced by fluctuations in body mass index).[20] Randomisation was carried out with the use of two strata: body mass index and axillary radiotherapy. Therefore, patients with a higher risk of developing breast cancer-related lymphoedema were equally divided between the experimental and control groups, thus reducing the potential for bias. Based on current knowledge, it would have been more correct to stratify for obesity and not for overweight (as was done in the present study). However, the proportion of participants with obesity at baseline was comparable in the experimental and control groups (20% versus 23%). Also, all non-stratified variables were comparable between groups. The number of patients who dropped out from the study was low. At 60 months after surgery, 83% of participants

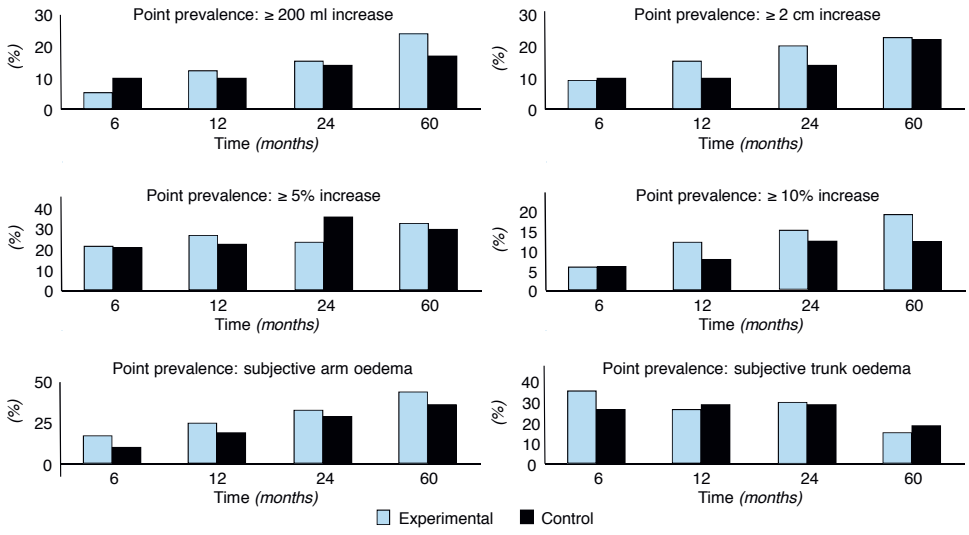

Figure 4. Point prevalence rates (%) of objective arm lymphoedema for the four definitions and of subjective arm and trunk lymphoedema at the different time intervals after surgery (months), with comparison between intervention group with manual lymph drainage (blue bar) and control group without manual lymph drainage (black bar).

were assessed. Only 17% or 27 participants dropped out. The main reason for drop-out was death or cancer recurrence.

This study had some limitations. The study population was not perfectly representative of all breast cancer patients. Compared to the study participants, excluded patients were about 3 years younger, had a body mass index about 1 higher, and were less likely to have received axillary radiotherapy. All other characteristics were comparable. MLD was started 5 weeks after axillary lymph node dissection, and frequency of MLD was one to three times a week. The participants did not perform self-MLD.

The potential preventive effect of MLD has to be further explored. In future studies, MLD should be started immediately after surgery, with the aim of stimulating the postoperative rerouting of the lymphatic system as soon as possible. To optimise the effect of MLD, the frequency of MLD application should be increased to 7 days a week. To make this more feasible, patients have to be instructed to perform self-MLD. In addition, a more efficient method of MLD has to be applied. For several years, near infrared florescence imaging has been used to visualise the superficial lymphatic architecture and function. It has been shown that other hand manoeuvres stimulate lymph transport more efficiently (eg, the fill and flush MLD drainage method).[37]

In current practice after axillary surgery for breast cancer, patients without lymphoedema still receive a lot of sessions of MLD. After the 6 months of physical treatment in the present study, a substantial proportion of participants from both groups consulted a physiotherapist to continue the MLD sessions, including some without lymphoedema who were not directed to do so. This suggests that some people may believe that any intervention must be beneficial. Therefore, it may be helpful to advise all patients, based on the results of this study, that there is not yet clear evidence to support or refute a long-term preventive effect from MLD. When patients without lymphoedema do receive many sessions of MLD, it is often at the expense of postoperative sessions of exercise therapy. Besides the stimulation of the lymphatic pump,[38] exercise therapy is necessary to prevent or treat dysfunctions of the upper limb developing after treatment of breast cancer.[39] The exercise therapy session should consist of passive mobilisations, stretch and transverse strain of breast muscles, and mobilising and stabilising exercises for the shoulder girdle and upper quadrant.[40]

In summary, this study highlights that the addition of MLD, applied from 1 month after surgery and with a frequency of one to three times a week, to information and exercise therapy may not have a substantial effect on the development of breast cancer-related lymphoedema in the short and long term.

What was already known on this topic: Lymphoedema is a common and disabling complication after breast cancer. Although some lymphoedema occurs early after breast cancer, it may also occur years later. Studies of manual lymph drainage after breast cancer have not followed participants long enough to adequately determine if there is a long-term preventive effect on lymphoedema. Despite this, some patients without lymphoedema choose to use manual lymph drainage with preventive intent.

What this study adds: Despite follow-up for 5 years, it remains uncertain whether manual lymph drainage for 6 months after treatment for breast cancer has a preventive effect on lymphoedema. Until the long-term preventive effect of manual lymph drainage is clear, patients without lymphoedema may consider spending their available therapy time on interventions with more robust evidence of preventive benefits, such as exercise.

Footnote: [a] SPSS Version 22.0, SPSS Inc, Chicago, IL, USA.

eAddenda: Table 9 can be found online at https://doi.org/10.1016/j.jphys.2018.08.007

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Competing interest: Nil.

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